Combinations of retigabine and sodium channel inhibitors or sodium channel-influencing active compounds for treating pains

The invention relates to pharmaceutical combinations of retiagbine and sodium channel inhibitors for treating pains which are accompanied by an increase in muscle tone.

A number of different painful diseases are accompanied by an increase in skeletal muscle tone. In some cases, the pain generation is elicited by joint inflammations, and a painful body posture, which is frequently accompanied by painful muscle spasms, develops as a consequence. The treatment of these diseases includes benzodiazepines, for example; however, these compounds possess a marked potential for addiction and this limits their use. Frequently, treating the basic disease, e.g. the rheumatoid inflammation, does not result in corresponding, satisfactory therapeutic successes. For this reason, the additional administration of analgesics and/or skeletal muscle relaxants is often indicated.

In clinical practice, centrally acting muscle relaxants are used for alleviating abnormally elevated muscle tone in patients who are suffering from painful muscle spasms and/or rigidity in association with rheumatoid diseases or spasms in connection with neurological diseases. While a number of appropriate active compounds are available on the market, their clinical efficacy is frequently questionable or else limited by undesirable side effects.

The Na^+ channel-inhibiting substances constitute one class of these active compounds. Evidence exists that these substances are able to relieve an increase in muscle tone. It has been shown that, in clinically relevant concentration, propofol has a marked

inhibitory effect on the sarcolemma sodium channels. This mechanism could contribute to reducing muscle tone (Haeseler et al., Anesth Analg 2001; 92:1192-8). It has also been shown that inhibiting the Na^+ channels inhibits neurotransmitter release from the presynaptic termini (Obrenovitch, Int Rev Neurobiol 1997; 40:109-35). The neuroprotective active compound riluzole is a sodium channel inhibitor and an antiexcitotoxic substance which is used for treating amyotrophic lateral sclerosis. Kennel et al. (J Neurol Sci 2000; 180:55-61) have recently shown that riluzole significantly delays the onset of the paralysis, and retards the progress of the functional parameters connected to muscle strength, in a mouse model of motoneuron disease. In a mouse model of heritable myotonia (De Luca et al., J Pharmacol Exp Ther 1997; 282:93-100), metilexin, an antiarrhythmic and antimyotonic substance, blocks the skeletal muscle sodium channels (Duranti et al., Eur J Med Chem 2000; 35:147-56) and relieves the hyperexcitability of the skeletal muscles. That the function of the skeletal muscle sodium channels is important in maintaining normal tone is supported by the fact that it has been possible to connect mutations in the gene for the α-subunit of the voltage-induced Na^+ channel (SCN4A) with inherited, nondystrophic myotonia. Interestingly, the myotonia resolved dramatically on administration of the Na^+ channel-inhibiting substance flecainide (Rosenfeld et al., Ann Neurol 1997; 42:811-4).

Tolperisone is a centrally acting muscle relaxant which is relatively well tolerated clinically. To date, relatively few publications have dealt with the mechanism of action of tolperisone-like compounds. Tolperisone suppresses transmission of the spinal segment reflex and effectively reduces C fiber-induced transmission in the afferent nerves both *in vivo* and *in vitro* (Farkas et al., Neurobiology 1997; 5:57-58). As compared with lidocaine, a local anesthetic, the

substance has less of a blocking effect on transmission in the A fibers. It characteristic effect is that of strongly inhibiting the monosynaptic and polysynaptic spinal reflexes (Farkas et al. Neurobiology 1997; 5:57-58, Kocsis et al., Acta Pharm Hung 2002; 72(1):49-61, Okada et al., Jpn J Pharmacol 2001; 86:134-136). In rats, Ono et al. (J Pharmacobio Dynam 1984; 7:171-178) showed that tolperisone exhibits an effect like that of a local anesthetic ("membrane-stabilizing") both in motor neurons and in primary afferents *in vivo* as well as on the peripheral nerves *in vitro*. The effect of tolperisone appears to be similar to that of lidocaine, which is known to act as an inhibitor of voltage-dependent sodium channels (Strathmann 2002, www.ifap-index.de/bda/hausarzt/19-2002/6483.pdf). It has been shown that tolperisone, like lidocaine, blocks the tetrodotoxin (TTX)-sensitive and TTX-resistant currents and in this way gives rise to an inhibitory effect on both types of voltage-dependent sodium channels (Bastigkeit, MMW-Forschr Med 2000; 142:50-51, Farkas et al., 2000, http://www.asso.univparis5.fr/ewcbr/Francais/EWCBR2000/Abstracts/ABST126.htm; Kocsis et al., Acta Pharm Hung 2002; 72(1):49-61). It is probable that the mechanism of action of tolperisone in this connection differs somewhat from that of lidocaine. In addition, evidence exists that tolperisone lowers sodium permeability. This effect could be responsible for the excitability-reducing effect of tolperisone and consequently for the antispastic effect which has been recorded in clinical observations (Hinck and Koppenhofer, Gen Physiol Biophys 2001; 20:413-29). In addition, voltage-clamp experiments performed on snail neurons showed that tolperisone and its analogs inhibit voltage-dependent calcium flows (Novalies-Li et al., Eur J Pharmacol 1989; 168:299-305). Tolperisone analogs such as eperisone and silperisone exhibited similar behavior in electrophysiological experiments. Thus, it has been shown, for example, that silperisone reduces sodium permeability (During and Koppenhofer, Gen

Physiol Biophys 2001; 20:157-73). It can be concluded from this that these substances might be able to reduce spastic skeletal muscle tone.

It has furthermore been shown, in clinical studies, that these substances are able to alleviate painful spasms which are associated with neurological or rheumatoid diseases. The effective employment of tolperisone in treating muscle spasms has been reported (Pratzel et al., Pain 1996; 67:417-25). Some derivatives of tolperisone, e.g. eperisone, also exhibited efficacy in the treatment of painful muscle spasms (Bose, Methods Find Exp Clin Pharmacol 1999; 21:209-13). Under certain pathological conditions, neurons are in a state of continuous depolarization, resulting in their sodium channels reacting more sensitively to the inhibitory effects of particular substances. This provides the possibility of alleviating muscle spasms and pain while preserving a favorable side-effect profile. More recent data indicate that tolperisone and its analogs exert selectively inhibitory effects on voltage-dependent sodium channels. This mechanism could be responsible for their spinal reflex-suppressing and muscle-relaxing effect. In addition, this property could produce the pain-alleviating effect which, because of the small differences which have been observed, could, in contrast to lidocaine, be free of side effects.

The potassium channel openers constitute another class of muscle-relaxing substances.
The substances include retigabine, for example. In *in vitro* analyses, it was shown that retigabine exerts multiple effects on sites which are connected with neurotransmission and membrane excitability. The primary mechanism of action appears to be based on a potassium channel opening which leads to marked stabilization of slightly depolarized, i.e. hyperexcitable cells and can result in an elevated

skeletal muscle tone being reduced (Rundfeldt and Netzer, Neurosci Letters 2000, 282:73-6).
Flupirtine is another representative of this substance class, which belongs to a class of triaminopyridines and which is used as a nonopioid analgesic possessing muscle-relaxing properties. It has been shown that flupirtine reduces skeletal muscle tone when it is used in doses which are comparable to those of the antinociceptive effect (Nickel et al., Arzn Forsch/Drug Res 1990a; 40:909-11).
More recent investigations demonstrate that flupirtine activates voltage-independent potassium channels (Kornhuber et al., J Neural Transm 1999; 106:857-67). This potassium channel-opening effect of flupirtine could be responsible for its analgesic and skeletal muscle-relaxing effect.

The prior art which has been described shows clearly that, while there are a number of substances which are used for treating pain conditions involving an increase in muscle tone, undesirable side effects frequently set limitations to their use. For example, at higher doses, flupirtine exhibits neurotoxic effects such as drowsiness and coordination disturbance. While tolperisone does not exhibit any severe undesirable side effects, its activity and the duration of its effect in connection with muscle relaxation are not satisfactory, possibly due to its relatively low bioavailability and its short half-life in humans (Ito et al., Arch Int Pharmacodyn Ther 1985; 275:105-22), Matsunaga et al., Jpn J Pharmacol 1997; 73:215-20).

The object of this invention is therefore that of providing a pharmaceutical for treating pains which are accompanied by an increase in muscle tone, which pharmaceutical exhibits less serious side effects while having a comparable efficacy or else exhibits a higher activity at the same dose.

According to the invention, it was possible to achieve this by means of the novel combination of retigabine and a sodium channel inhibitor.

It was possible to show that the combination of sodium channel-inhibiting or -influencing active compounds and potassium channel openers increases the muscle-relaxing effect.

The following may, for example, be employed as Na^+ channel-inhibiting or -influencing substances: tolperisone and its analogs eperisone and silperisone, riluzole, propafenone, lidocaine, flecainide and metixen, as well as their pharmaceutically utilizable salts.

Particular preference is given, in this connection, to the combination of tolperisone, or its analogs, and retigabine, or their pharmaceutically utilizable salts.

The combination according to the invention makes the treatment of pains which are accompanied by an increase in muscle tone more effective and more reliable. The combination of Na-channel inhibiting or -influencing substances and retigabine leads either to an increase in the therapeutic effect or an improvement in tolerability. For example, it has been shown that Na channel-inhibiting or -influencing active compounds such as tolperisone can amplify the muscle-relaxing effect of retigabine, and vice versa. However, what is surprising, and unexpected for the skilled person, is, in particular, the effect that tolperisone superadditively amplifies the skeletal muscle-relaxing effect of retigabine and vice versa. By contrast, tolperisone does not amplify the side effects of retigabine.

The combination of the two substances can be used for treating pains in connection with diseases of the skeletal musculature which are accompanied by hypermyotonia and restricted mobility, in particular those which are elicited by injuries to the spinal cord, osteoporosis, arthritis and ankylosis/spastic

conditions. It is also effective in connection with pains of the following origin: lumboischial pains, neurolathyrism, arthritis, diseases of the peripheral circulatory system, climacteric muscular and vascular complaints, trismus, myogenic headaches, rheumatic diseases which are accompanied by muscle hypertonia, spasms, pain, inflammatory symptoms and restricted mobility, and multiple sclerosis, and in the postoperative treatment of traumatic patients and for treating lower spastic paraparesis syndrome: lower paraspasm, transverse myelitis, multiple sclerosis, heritable inferior spastic paraplegia (Stuempel paraplegia), disturbances of the spinal blood circulation, cerebral paralysis involving lower spastic paresis, tetraparesis in connection with cervical myelopathy, vertebral dysplasia, tension headache and cervical brachialgia.

The combinations of Na^+ channel-inhibiting or -influencing active compounds and retigabine, and of their pharmaceutically utilizable salts, can be administered in all oral, enteral, rectal, lingual, intravenous, intramuscular, intraperitoneal, transdermal, subcutaneous or intracutaneous administration forms. Examples of preferred oral administration forms are tablets, film-coated tablets, sugar-coated tablets, hard gelatin capsules, soft gelatin capsules, chewing tablets, sucking tablets, syrup, controlled release preparations (for example dual formulation, delayed-release formulation), pellets, chewing tablets or soluble granules. Examples of other suitable administration forms are: solutions for injection, suspensions, suppositories, creams, ointments, gels, transdermal administration forms and subcutaneous or intracutaneous implants.

The substances can be administered simultaneously, consecutively or in a fixed combination. They can be administered together in one administration form or in two administration forms which can be identical or

different. They can be administered simultaneously or consecutively, either briefly one after the other or at longer time intervals, for example retigabine in the evening and tolperisone in the morning.

The active compounds can be administered between 1 and 8 times daily, in an adequate quantity to achieve the desired affect. The active compounds are preferably administered from once to four times daily.

The daily dose should correspond to the approved quantities of the substances which are in each case employed in the combination.